PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 7/22, A23G 3/30 — A1

(11) International Publication Number: WO 94/18939

(43) International Publication Date: 1 September 1994 (01.09.94)

(21) International Application Number: PCT/US94/01316

(22) International Filing Date: 4 February 1994 (04.02.94)

(30) Priority Data:
08/019,737 19 February 1993 (19.02.93) US

(71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors: CARLIN, Edward; 794 5th Street, Secaucus, NJ 07094 (US). CHU, Paula; 19 McCann Mill Road, Pottersville, NJ 07979 (US). DILLS, Steven, S.; 18 Elmwood Drive, Hackettstown, NJ 07840 (US). TALWAR, Anil; 75 East Mill Road, Long Valley, NJ 07853 (US).

(74) Agents: ALMER, Charles, W., III et al.; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US).

(81) Designated States: AU, CA, JP, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PRE-BRUSHING RINSE COMPOSITION

(57) Abstract

This invention relates to an efficacious pre-brushing anti-plaque, anti-gingivitis rinse or other dental hygiene compositions comprising essential oil(s) and an antimicrobial, antiseptic quaternary ammonium salt detergent such as cetylpyridinium chloride. Daily treatment with the dental hygiene product shows improved removal of supra-gingival accumulation of plaque.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

PRE-BRUSHING RINSE COMPOSITION

FIELD OF THE INVENTION

The present invention relates to a composition for oral use such as, in particular, clinically efficacious anti-plaque, anti-gingivitis mouth wash, mouth rinse, toothpaste, chewing gum or dentifrice.

BACKGROUND OF THE INVENTION

It is well known that in the course of time plaque or calculus deposits (commonly referred to as tartar) tend to accumulate on surfaces of teeth, particularly at the gingival margin. Although the degree and speed of this supragingival accumulation varies with the individual it is generally found on the lingual surfaces of the lower anterior teeth and on the buccal sides of the upper first and second molars, as well as on the distal parts of the posterior molars. The calculus deposit or plaque matures as an inorganic portion of mostly calcium phosphate forming a hydroxyapatite lattice structure similar to the biological formation of bone, enamel and denture. In addition, the deposit also contains an organic component which consists of desquamated epithelial cells, leukocytes, salivary sediment, food debris and several different microorganisms.

While the discoloration of the teeth due to the yellowish appearance of the mature calculus is aesthetically highly unpleasant and undesirable, the presence of this stone-like build-up tends to lead to an irritation of the adjacent tissue, with subsequent tissue inflammation and swelling, followed by loosening of the affected teeth, and increased exposure of the teeth to bacterial attack or caries. Furthermore, the inflammation of tissue produces secretion of specific collagen proteases leading the way for bacterial proteolytic erosion of the collagen matrix at the gingival margin of the teeth.

In the past, a considerable number of procedures and remedial agents have been applied or at least suggested in order to retard the rate of formation of calculus and perhaps remove the deposited layer. Mechanical cleaning to remove the deposited calculus is now routine dental procedure. There are also chemical methods for preventing or even reducing calculus formation on teeth that utilize calcium-chelating agents to remove calcium from the calculus composition and thereby prevent crystallite formation. Specifically, the state of the art treatment has included use of oral compositions containing EDTA (ethylenediaminetetra acid), fluoride and certain di- or polyphosphonates, and various surfactant preparations.

Moreover, the known anticalculus compositions and treatments include polyelectrolytes with polyacrylics ranging in molecular weight from 2,000 to 4,000,000 forming a protective coating membrane on the tooth surface to keep either medical reagents from being washed off or salivary materials from attaching to the tooth surface. However, while these methods constitute improvements in the preventive care of teeth, there is to our knowledge no clinically efficacious pre-brushing rinse available that substantially reduces plaque.

It is therefore an object of the present invention to provide an improved therapeutic dental composition or a final product for effectively and significantly removing or preventing dental calculus, without the need for mechanical cleaning of the tooth surface.

It is a further object of the present invention to provide a mouth rinse that would efficaciously retard plaque accumulation upon regular use; in particular, it is the object of the present invention to provide a composition containing therapeutically effective concentrations of combinations of cationic surfactants such as quaternary ammonium salts with essential oils.

SUMMARY OF THE INVENTION

The present invention is directed to a dental hygiene composition or final product containing a combination of at least one essential oil and an antiseptic or antimicrobial quaternary ammonium salt detergent such as benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, domiphen bromide, 1-(3-chlorallyl)-3,5-7-triaza-1-azoniaadamentane chloride, or menthene ammonium chloride. In particular, the composition is directed to therapeutically effective mouth rinse or mouthwash solution for the treatment of calculus or plaque in order to prevent gingivitis.

An especially preferred embodiment of the present invention combines essential oils such as peppermint, thymol, and eucalyptol with an antimicrobial quaternary ammonium salt such as cetylpyridinium chloride in addition to various optional ingredients as known in the art in an ethanol/water solution.

DETAILED DESCRIPTION OF THE INVENTION

The oral composition useful in the treatment of plaque or gingivitis according to the present invention can be used to rinse the mouth and teeth such that plaque (also called tartar or calculus) separately from any brushing or

other suitable mechanical cleansing procedure can be prevented from accumulating thereby causing gingivitis and subsequent tooth destruction or loss. Moreover, the daily oral dental hygiene treatment with anti-plaque, anti-gingivitis mouthwash or mouthrinse according to the present invention has been found to be surprisingly effective in retarding and even removing pre-existing calculus with regular use, over time.

In sum, the clinically effective anti-plaque, anti-gingivitis rinsing solution of the present invention has been shown to be efficacious in the therapy of gingivitis such that after twice daily treatment:

1. Plaque is removed when used prior to mechanical cleaning thereby augmenting or facilitating the desirable effect of some known cleaning methods such as manual brushing;

2. Plaque is prevented from regrowing when used as follow-up to mechanical cleaning methods, augmenting the desirable effect of mechanical cleaning method such as by post-brushing rinse;

3. Plaque is reduced or prevented from growing even in the absence of other methods of oral hygiene.

"Oral composition" as defined herein pertains to a product (final or intermediate) which is not necessarily

intended to be ingested but to be retained in the oral cavity, especially near or on the teeth's surfaces for a time sufficient for full contact and oral activity. "Oral vehicle" as defined herein pertains to food grade ingestible or pharmaceutically acceptable material, suitable for applying the inventive composition in the oral cavity.

Essential oils are volatile oils or essences derived from plants and usually carry the odor or flavor of the plant obtained by distillation, expression or extraction. The essential oils of the present invention include but are not limited to menthol, carvone, anethole, eugenol, isoeugenol, methyl salicylate, limonene, osimen, n-decyl alcohol, citronel, a-salpineol, methyl acetate, citronellyl acetate, methyl eugenol, cineol, linalool, ethyl linalool, safrola vanillin, thymol, spearmint oil, peppermint oil, lemon oil, orange oil, sage oil, rosemary oil, cinnamon oil, pimento oil, laurel oil, beefleaf oil, wintergreen oil, clove oil, and eucalyptus oil.

Thymol, also known by the chemical formula 5-methyl 2- (1 methylethyl) phenol, is obtained from the essential oil of Thymus vulgari L. and Monarda punctata L., Labiatae. Thymol is a white crystalline powder with an aromatic odor and taste and is soluble in organic solvents but only slightly soluble in pure deionized water.

Menthol is isolated principally from the oil of Mentha arvensis. In its commercial form, menthol is present as L-menthol crystals obtained from a process involving cooling of the oil. Fractional distillation of peppermint oil which usually contains from about 50% to about 65% menthol provides another important source of menthol. Synthetic sources of L-menthol are also available.

The use of menthol for its medicinal effects is known in the art. Menthol's cooling effect to the mouth is useful to relieve local irritations in the throat and mouth.

Eucalyptus oil mainly consisting of eucalyptol is another volatile oil thought to have therapeutic properties and is derived from the eucalyptus tree. Having a camphoraceous odor and cooling taste, this volatile oil is often combined with other essential oils such as those of menthol in confection formulations to impart medicinal effect. Combinations of menthol and eucalyptus are widely used. They are included in formulations capable of dissolving in the oral cavity. Other uses of the menthol/eucalyptus combination include mouthwashes, mouthrinses, and dentifrices.

In one preferred dental hygiene embodiment of the invention, the oral anti-plaque, anti-gingivitis

composition includes an oral vehicle and is in the form of a liquid such as a mouthwash, rinse or oral spray. The concentration of the essential oil(s) ranges by weight from about 0.01% to about 1.0%.

Typical non-toxic oral carrier vehicles known in the dental art may be used in the present invention. Preferred vehicles include water and water-alcohol mixtures. The water-alcohol mixtures are generally employed in a weight ratio from about 1:1 to about 20:1, preferably from about 3:1 to about 20:1, and most preferably from about 3:1 to about 10:1, respectively. The pH value of the vehicle is generally from about 3.0 to about 7, and preferably from about 4 to about 4.5. A vehicle having a pH value below about 3 is generally found as irritating to the oral cavity. A vehicle having a pH value greater than about 7 generally results in an unpleasant mouth feel.

The preferred embodiments of mouthwashes, rinses and dentifrice of the present invention may contain conventional additives normally employed in liquid oral anti-plaque, anti-gingivitis compositions. These additives include sorbitol solution, a surfactant, a fluorine providing compound, a sweetening agent, a flavoring agent, a coloring agent, a humectant, a buffer, and the like, providing the additives do not interfere with the anti-

plaque, anti-gingivitis properties of the composition of the present invention.

The liquid oral clinically effective anti-plaque, anti-gingivitis composition of the present invention may contain sorbitol or sorbitol solution in high weight to volume concentrations (w/v), i.e., from about 20% to about 75% w/v, and preferably from about 50% to about 60% w/v, of sorbitol solution, U.S. Pharmacopeia, which is a solution of sorbitol in water containing 70% total solids. Sorbitol solution supplies sweetness and body to the composition and gives a desirable mouth feel. Sorbitol solution also enhances flavor, prevents harsh taste and provides a fresh and lively sensation in the mouth.

Surfactants (surface active agents) are organic compounds which reduce surface tension between liquids and aid in the dispersion of a composition throughout the oral cavity. The surfactant in the present invention may be nonionic, ampholytic, or cationic. The liquid oral anti-plaque, anti-gingivitis compositions of the present invention may contain surfactants in amounts up to about 5%, and preferably from about 0.05% to about 2%, by weight of the oral liquid anti-plaque, anti-gingivitis composition.

Suitable nonionic surfactants in the present invention include poly(oxyethylene)-poly(oxypropylene)

block copolymers. Such copolymers are known commercially by the non-proprietary name of poloxamers, which name is used in conjunction with a numeric suffix to designate the individual identification of each copolymer. Poloxamers may have varying contents of ethylene oxide and propylene oxide which results in poloxamers which have a wide range of chemical structures and molecular weights. The nonionic poloxamer surfactants of the present invention are non-toxic, are acceptable as direct food additives, are stable, readily dispersible in aqueous systems and are compatible with the wide variety of formulating ingredients used in oral compositions.

Poloxamer surfactants in the present invention should have a Hydrophilic-Lipophilic Balance (HLB) of between about 10 and about 30, and preferably between about 10 and about 25. Suitable poloxamers in this invention include: Poloxamers 105, 108, 123, 124, 183, 184, 185, 188, 215, 217, 234, 235, 237, 238, 284, 288, 334, 335, 338, and 407. A particularly preferred poloxamer is Poloxamer 407, which has an HLB of about 22, and is sold under the tradename Pluronic F-127 by BASF Wyandotte, Parsippany, N.J. When present in the liquid oral anti-plaque, anti-gingivitis composition, poloxamers should constitute from about 0.01% to about 1%, and preferably from about 0.05% to

about 5%, by weight of the total volume of liquid oral anti-plaque, anti-gingivitis composition (w/v).

Another class of nonionic surfactants useful in this invention are the ethoxylated hydrogenated castor oils. These surfactants are prepared by hydrogenating castor oil and treating the hydrogenated product with from about 10 to about 200 moles of ethylene glycol. These ethoxylated hydrogenated castor oils are known by the non-proprietary name of PEG hydrogenated castor oils, in accordance with the dictionary of the Cosmetics, Toiletries and Fragrance Association, 3rd Edition, which name is used in conjunction with a numeric suffix to designate the degree of ethoxylation of the hydrogenated castor oil product, i.e., the number of moles of ethylene oxide added to the hydrogenated castor oil product. Suitable PEG hydrogenated castor oils include PEG 16, 20, 25, 30, 40, 50, 60, 80, 100, and 200. In a preferred embodiment, the PEG hydrogenated castor oil surfactant is Cremophor RH40, a commercially available product from BASF-Wyandotte, Parsippany, N.J. Ethoxylated hydrogenated castor oil surfactants, when present in the liquid oral dental hygiene composition for combatting plaque and gingivitis, should constitute from about 0.2% to about 2%, and preferably from about 0.5% to about 1%, by weight of the total volume

of liquid oral anti-plaque, anti-gingivitis composition (w/v).

Other nonionic surfactants useful in the present invention include condensates of sorbitan esters of fatty acids with ethylene oxide (polysorbates) such as sorbitan mono-oleate with from about 20 to about 60 mole percent of ethylene oxide (e.g., "Tweens," a trademark of ICI U.S., Inc.) Particularly preferred polysorbates are Polysorbate 20 (polyoxyethylene 20 sorbitan monolaurate, Tween 20) and Polysorbate 80 (polyoxyethylene 20 sorbitan mono-oleate, Tween 80).

Additional suitable nonionic surfactants useful in the present invention are the condensation products of an alpha-olefin oxide containing 10 to 20 carbon atoms, a polyhydric alcohol containing 2 to 10 carbon atoms and 2 to 6 hydroxyl groups, and either ethylene oxide or a mixture of ethylene oxide and propylene oxide. The resultant surfactants are polymers which have a molecular weight in the range from about 400 to about 1600, contain from about 40% to about 80% ethylene oxide, by weight, and have an alpha-olefin oxide to polyhydric alcohol mole ratio in the range from about 1:1 to about 1:3, respectively.

Other nonionic surfactants useful in the present invention include condensates of sorbitan esters of fatty acids with polyethylene glycol such as sorbitan

diisostearate condensed with polyethylene glycol. A particularly preferred polyethylene glycol condensate of a diisostearate sorbate ester is EmSorb 2726, a commercially available product manufactured by Emery Industries Incorporated, Linden, N.J.

Amphoteric surfactants have the capacity to behave as either an acid or a base. Amphoteric surfactants useful in the present invention include quaternized imidazole derivatives.

Cationic surfactants are surfactants which carry a positive charge. Cationic surfactants especially useful in the present invention include antimicrobial quaternary ammonium salts. This class of compounds can be illustrated but not limited to, cetylpyridinium chloride, benzalkonium chloride, benzethonium chloride, domiphen bromide, 1-(3-chlorallyl)-3,5-7-triaza-1-azoniaadamantane chloride, and menthene ammonium chloride. The most preferred embodiment of the present invention includes cetylpyridinium chloride. A preferred embodiment of the present invention provides antimicrobial quaternary ammonium salt detergent ranging from about 0.005% to about 8%.

Fluorine providing compounds may be fully or slightly water soluble and are characterized by their ability to release fluoride ions or fluoride containing ions in water and by their lack of reaction with other

components in the composition. Typical fluorine providing compounds are inorganic fluoride salts such as water-soluble alkali metal, alkaline earth metal, and heavy metal salts, for example, sodium fluoride, potassium fluoride, ammonium fluoride, cuprous fluoride, zinc fluoride, stannic fluoride, stannous fluoride, barium fluoride, sodium fluorosilicate, ammonium fluorosilicate, sodium fluorozirconate, sodium monofluorophosphate, aluminum mono- and difluorophosphates and fluorinated sodium calcium pyrophosphate. Alkali metal fluorides, tin fluoride and monofluorophosphates, such as sodium and stannous fluoride, sodium monofluorophosphate and mixtures thereof, are preferred.

The amount of fluorine providing compound present in a preferred embodiment of the liquid oral anti-plaque, anti-gingivitis composition is dependent upon the type of fluorine providing compound employed, the solubility of the fluorine compound, and the nature of the final liquid oral anti-plaque, anti-gingivitis composition. The amount of fluorine providing compound used must be a nontoxic amount. In general, the fluorine providing compound when used will be present in an amount up to about 1%, preferably from about 0.001% to about 0.1%, and most preferably from about 0.001% to about 0.05%, by weight of the oral liquid anti-plaque, anti-gingivitis composition.

When sweetening agents (sweeteners) are used, those sweeteners well-known in the art, including both natural and artificial sweeteners, may be employed. The sweetening agent used may be selected from a wide range of materials including water-soluble sweetening agents, water-soluble artificial sweetening agents, water-soluble sweetening agents derived from naturally occurring water-soluble sweetening agents, dipeptide based sweetening agents, and protein based sweetening agents, including mixtures thereof. Without being limited to particular sweetening agents, representative categories and examples include:

(a) water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, glycyrrhizin, and sugar alcohols such as sorbitol, mannitol, maltitol, hydrogenated starch hydrolysates and mixtures thereof;

(b) water-soluble artificial sweeteners such as soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl - 1,2,3-oxathiazine-4-one-2,

2-dioxide, the potassium salt of 3,4-dihydro-6-methyl - 1,2,3-oxathiazine-4-one-2, 2-dioxide (Acesulfame-K), the free acid form of saccharin, and the like;

(c) dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (Aspartame) and materials described in U.S. Pat. No. 3,492,131, L-alphaaspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alani namide hydrate (Alitame), methyl esters of L-aspartyl-L-phenylglycerine and L-aspartyl-L-2,5-dihydrophenylglycine, L-aspartyl-2,5-dihydro-L-phenylalanine; L-aspartyl-L-(1-cyclohexen)-alanine, and the like;

(d) water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as chlorinated derivatives of ordinary sugar (sucrose), known, for example, under the product designation of Sucralose; and

(e) protein based sweeteners such as thaumaoccous danielli (Thaumatin I and II).

In general, an effective amount of sweetening agent is utilized to provide the level of sweetness desired in any particular oral anti-plaque, anti-gingivitis compositions, and this amount will vary with the sweetener selected and the final oral anti-plaque, anti-gingivitis

product. The amount of sweetener normally present is in the range from about 0.0025% to about 90%, by weight of the embodiment of the oral anti-plaque, anti-gingivitis composition such as mouthwash or rinse, depending upon the sweetener used. The exact range of amounts for each type of sweetener is well known in the art and is not the subject of the present invention. The flavoring agents (flavors, flavorants) which may be used include those flavors known to the skilled artisan, such as natural and artificial flavors. Suitable flavoring agents include mints, such as peppermint, citrus flavors such as orange and lemon, artificial vanilla, cinnamon, various fruit flavors, both individual and mixed and the like.

The amount of flavoring agent employed herein is normally a matter of preference subject to such factors as the type of final liquid oral anti-plaque, anti-gingivitis composition, the individual flavor employed, and the strength of flavor desired. Thus, the amount of flavoring may be varied in order to obtain the result desired in the final product and such variations are within the capabilities of those skilled in the art without the need for undue experimentation. The flavoring agents, when used, are generally utilized in amounts that may, for example, range in amounts from about 0.05% to about 6%, by

weight of the liquid oral anti-plaque, anti-gingivitis composition.

The coloring agents (colors, colorants) useful in the present invention are used in amounts effective to produce the desired color. These coloring agents include pigments which may be incorporated in amounts up to about 6%, by weight of the liquid oral anti-plaque, anti-gingivitis composition. A preferred pigment, titanium dioxide, may be incorporated in amounts up to about 2%, and preferably less than about 1%, by weight of the composition. The colorants may also include natural food colors and dyes suitable for food, drug and cosmetic applications. These colorants are known as F. D. & C dyes and lakes. The materials acceptable for the foregoing uses are preferably water-soluble. Illustrative nonlimiting examples include the indigoid dye known as F. D. & C Blue No.2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye known as F. D. & C Green No.1 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-(N-ethyl-p-sulfoniumbenzylamino) diphenylmethylene]-[1-(N-ethyl-N-p-sulfoniumbenzyl)-delta-2,5- cyclohexadieneimine]. A full recitation of all F.D.& C colorants and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical

Technology, 3rd Edition, in volume 5 at pages 857-884, which text is incorporated herein by reference.

Suitable humectants in the present invention include glycerin, propylene glycol, polyethylene glycol, sorbitan, fructose, mixtures thereof and the like. Humectants, when employed, may be present in amounts from about 10% to about 20%, by weight of the liquid oral anti-plaque, anti-gingivitis composition.

Suitable buffers in the present invention include citric acid-sodium citrate, phosphoric acid-sodium phosphate, acetic acid-sodium acetate and benzoic acid and benzoate in amounts up to about 1%, and preferably from about 0.05% to about 0.5%, by weight of the liquid oral anti-plaque, anti-gingivitis composition for dental hygiene.

The present invention extends to methods of making the improved liquid oral antiseptic compositions. The final compositions are readily prepared using methods generally known by those skilled in the dental art. In such a method, an oral antiseptic composition, according to the present invention is made by first dissolving the surfactant, cetylpyridinium chloride, in water, then admixing sorbitol or sorbitol solution to the surfactant solution until the sorbitol is dissolved. Coloring agents, additional sweetening agents, and similar additives are

admixed at the same time sorbitol is added. The peppermint oil, eucalyptol, and thymol are then admixed to the surfactant/sorbitol solution until dissolved. The pH value of the solution is adjusted to 4-6 using 1-N hydrochloric acid or 1-N sodium hydroxide. Then sufficient water or alcohol, or mixtures thereof are added to the solution with mixing until the final solution volume is reached. In a preferred embodiment, the peppermint oil, eucalyptol, and thymol are added to the solution in the alcohol portion.

The apparatus useful in accordance with the present invention comprises mixing apparatus well known in the dental art, and therefore the selection of the specific apparatus will be apparent to the artisan.

In another form of the invention, the oral anti-plaque, anti-gingivitis composition includes an oral vehicle and is in the form of a dental gel. As used herein, the term "gel" means a solid or semisolid colloid which contains considerable quantities of water. The colloid particles in a gel are linked together in a coherent meshwork which immobilizes the water contained inside the meshwork.

In the dental gel compositions, the oral vehicle generally comprises water, typically in an amount from about 10% to about 90%, by weight of the dental gel composition. Polyethylene glycol, propylene glycol,

glycerin, sorbitol or mixtures thereof may also be present in the vehicle as humectants or binders in amounts from about 18% to about 30%, by weight of the dental gel composition. Particularly preferred oral vehicles comprise mixtures of water with polyethylene glycol or water with glycerin and polypropylene glycol.

The dental gels of the present invention include a gelling agent (thickening agent) such as a natural or synthetic gum. Gelling agents such as hydroxyethyl cellulose, methyl cellulose and the like may be used. The preferred gelling agent is hydroxyethyl cellulose. Gelling agents may be used in amounts from about 0.5% to about 5%, and preferably from about 0.5% to about 2%, by weight of the dental gel composition.

The dental gel compositions of the present invention may contain the conventional additives set out above for mouthwash and spray anti-plaque, anti-gingivitis compositions and, in addition, may contain additional conventional additives such as a polishing agent, a desensitizing agent, a preservative and the like, providing the additives do not interfere with the anti-plaque, anti-gingivitis properties of the composition. The sorbitol solution, surfactants, fluorine providing compounds, sweetening agents, flavoring agents, coloring agents, humectants, buffers set out above as useful in the

mouthwash and spray liquid oral anti-plaque, anti-gingivitis compositions may also be utilized in the dental gel compositions.

The dental gel compositions of the present invention may also include a polishing agent. In clear gels, a polishing agent of colloidal silica and/or alkali metal aluminosilicate complexes is preferred since these materials have refractive indices close to the refractive indices of the gelling systems commonly used in dental gels. In non-clear gels, a polishing agent of calcium carbonate or calcium dihydrate may be used. These polishing agents may be used in amounts up to about 75%, and preferably in amounts up to about 50%, by weight of the dental gel composition.

The dental gel may also contain a desensitizing agent such as a combination of citric acid and sodium citrate. Citric acid may be used in an amount from about 0.1% to about 3%, and preferably from about 0.2% to about 1%, by weight, and sodium citrate may be used in an amount from about 0.3% to about 9%, and preferably from about 0.6% to about 3%, by weight of the dental gel composition.

Suitable preservatives in the present invention include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, methyl paraben, propyl paraben, tocopherols and mixtures thereof. Preservatives

when used are generally present in amounts up to about 1.0%, and preferably from about 0.1% to about 1.0%, by weight of the dental gel composition.

Another important aspect of the present invention includes an anti-plaque, anti-gingivitis chewing gum composition incorporating the inventive pre-brushing anti-plaque, anti-gingivitis composition and a method for preparing the chewing gum composition, including both chewing gum and bubble gum formulations. In this form of the invention, the chewing gum composition contains a gum base, the anti-plaque, anti-gingivitis composition, and various additives.

The gum base employed will vary greatly depending upon various factors such as the type of base desired, the consistency of gum desired and the other components used in the composition to make the final chewing gum product. The gum base may be any water-insoluble gum base known in the art, and includes those gum bases utilized for chewing gums and bubble gums. Illustrative examples of suitable polymers in gum bases include both natural and synthetic elastomers and rubbers. For example, those polymers which are suitable as gum bases include, without limitation, substances of vegetable origin such as chicle, crown gum, nispero, rosadinha, jelutong, perillo, niger gutta, tunu, balata, gutta-percha, lechi-capsi, sorva, gutta kay,

mixtures thereof and the like. Synthetic elastomers such as butadiene-styrene copolymers, polyisobutylene, isobutylene-isoprene copolymers, polyethylene, mixtures thereof and the like are particularly useful.

The gum base may include a non-toxic vinyl polymer, such as polyvinyl acetate and its partial hydrolysate, polyvinyl alcohol, and mixtures thereof. When utilized, the molecular weight of the vinyl polymer may range from about 3,000 up to and including about 94,000.

The amount of gum base employed will vary greatly depending upon various factors such as the type of base used, the consistency of the gum desired and the other components used in the composition to make the final anti-plaque, anti-gingivitis effective chewing gum product. In general, the gum base will be present in amounts from about 5% to about 94%, by weight of the final chewing gum composition, and preferably in amounts from about 15% to about 45%, and more preferably in amounts from about 15% to about 35%, and most preferably in amounts from about 20% to about 30%, by weight of the final anti-plaque, anti-gingivitis chewing gum composition.

The gum base composition may contain conventional elastomer solvents to aid in softening the elastomer base component. Such elastomer solvents may comprise terpinene resins such as polymers of alphapinene or beta-pinene,

methyl, glycerol or pentaerythritol esters of rosins or modified rosins and gums, such as hydrogenated, dimerized or polymerized rosins or mixtures thereof. Examples of elastomer solvents suitable for use herein include the pentaerythritol ester of partially hydrogenated wood or gum rosin, the pentaerythritol ester of wood or gum rosin, the glycerol ester of wood rosin, the glycerol ester of partially dimerized wood or gum rosin, the glycerol ester of polymerized wood or gum rosin, the glycerol ester of tall oil rosin, the glycerol ester of wood or gum rosin and the partially hydrogenated wood or gum rosin and the partially hydrogenated methyl ester of wood or rosin, mixtures thereof, and the like. The elastomer solvent may be employed in amounts from about 5.0% to about 75.0%, by weight of the gum base, and preferably from about 45.0% to about 70.0%, by weight of the gum base.

A variety of traditional ingredients may be included in the gum base in effective amounts such as plasticizers or softeners such as lanolin, palmitic acid, oleic acid, stearic acid, sodium stearate, potassium stearate, glycerol triacetate, glycerol lecithin, glycerol monostearate, propylene glycol monostearate, acetylated monoglyceride, glycerine, mixtures thereof, and the like may also be incorporated into the gum base to obtain a variety of desirable textures and consistency properties.

Waxes, for example, natural and synthetic waxes, hydrogenated vegetable oils, petroleum waxes such as polyurethane waxes, polyethylene waxes, paraffin waxes, microcrystalline waxes, fatty waxes, sorbitan monostearate, tallow, propylene glycol, mixtures thereof, and the like may also be incorporated into the gum base to obtain a variety of desirable textures and consistency properties. These traditional additional materials are generally employed in amounts up to about 30.0%, by weight of the gum base, and preferably in amounts from about 3% to about 20%, by weight of the gum base. The gum base may include effective amounts of mineral adjuvants such as calcium carbonate, magnesium carbonate, alumina, aluminum hydroxide, aluminum silicate, talc, tricalcium phosphate, dicalcium phosphate and the like as well as mixtures thereof. These mineral adjuvants may serve as fillers and textural agents. These fillers or adjuvants may be used in the gum base in various amounts. Preferably the amount of filler when used will be present in an amount from greater than about 0% to about 60%, by weight of the chewing gum base.

The chewing gum base may additionally include the conventional additives of coloring agents, antioxidants, preservatives and the like. For example, titanium dioxide and other dyes suitable for food, drug and cosmetic

applications, known as F.D. & C dyes, may be utilized. An anti-oxidant such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, and mixtures thereof, may also be included. Other conventional chewing gum additives known to one having ordinary skill in the chewing gum art may also be used in the chewing gum base.

The gum composition may include effective amounts of conventional additives selected from the group consisting of sweetening agents (sweeteners), plasticizers, softeners, emulsifiers, waxes, fillers, bulking agents, mineral adjuvants, flavoring agents (flavors, flavorings), coloring agents (colorants, colorings), antioxidants, acidulants, thickeners, mixtures thereof and the like. Some of these additives may serve more than one purpose. For example, in sugarless gum compositions, the sweetener, e.g., sorbitol or other sugar alcohol or mixtures thereof, may also function as a bulking agent. Similarly, in sugar containing gum compositions, the sugar sweetener can also function as a bulking agent.

The plasticizers, softeners, mineral adjuvants, colorants, waxes and antioxidants discussed above as being suitable for use in the gum base may also be used in the gum composition. Examples of other conventional additives which may be used include emulsifiers, such as lecithin and

glycerol monostearate, thickeners, used alone or in combination with other softeners, such as methyl cellulose, alginates, carrageenan, xanthin gum, gelatin, carob, tragacanth, locust bean, and carboxy methyl cellulose, acidulants such as malic acid, adipic acid, citric acid, tartaric acid, fumaric acid, and mixtures thereof, and fillers, such as those discussed above under the category of mineral adjuvants. The fillers when used may be utilized in an amount from greater than about 0% to about 60%, by weight of the gum composition.

Bulking agents (carriers, extenders) suitable for use include sweetening agents selected from the group consisting of monosaccharides, disaccharides, polysaccharides, sugar alcohols, and mixtures thereof; polydextrose; maltodextrins; minerals, such as calcium carbonate, talc, titanium dioxide, dicalcium phosphate, and the like. Bulking agents may be used in amounts up to about 90%, by weight of the final gum composition, with amounts from about 40% to about 70%, by weight of the gum composition being preferred, with from about 50% to about 65%, by weight, being more preferred and from about 55% to about 60%, by weight of the chewing gum composition, being most preferred.

In general, an effective amount of sweetener is utilized to provide the level of bulk and/or sweetness

desired, and this amount will vary with the sweetener selected. This amount of sweetener will normally be present in amounts from about 0.0025% to about 90%, by weight of the gum composition, depending upon the sweetener used. The exact range of amounts for each type of sweetener is well known in the art and is not the subject of the present invention. The amount of sweetener ordinarily necessary to achieve the desired level of sweetness is independent from the flavor level achieved from flavor oils.

Preferred sugar based-sweeteners are sugar (sucrose), corn syrup and mixtures thereof. Preferred sugarless sweeteners are the sugar alcohols, artificial sweeteners, dipeptide based sweeteners and mixtures thereof. Preferably, sugar alcohols are used in the sugarless compositions because these sweeteners can be used in amounts which are sufficient to provide bulk as well as the desired level of sweetness. Preferred sugar alcohols are selected from the group consisting of sorbitol, xylitol, maltitol, mannitol, and mixtures thereof. More preferably, sorbitol or a mixture of sorbitol and mannitol is utilized. The gamma form of sorbitol is preferred. An artificial sweetener or dipeptide based sweetener is preferably added to the gum compositions which contain sugar alcohols.

Suitable oils and fats usable in gum compositions include partially hydrogenated vegetable or animal fats, such as coconut oil, palm kernel oil, beef tallow, lard, and the like. These ingredients when used are generally present in amounts up to about 7.0%, by weight, and preferably up to about 3.5%, by weight of the gum composition.

The anti-plaque, anti-gingivitis effective compositions according to the preferred invention may be incorporated into an otherwise conventional chewing gum composition using standard techniques and equipment known to those skilled in the art. For example, a gum base is heated to a temperature sufficiently high enough to soften the base without adversely effecting the physical and chemical make up of the base. The optimum temperatures utilized may vary depending upon the composition of the gum base used, but such temperatures are readily determined by those skilled in the art without undue experimentation.

The gum base is conventionally melted at temperatures that range from about 60° C to about 120° C for a period of time sufficient to render the base molten. For example, the gum base may be heated under these conditions for a period of about thirty minutes just prior to being admixed incrementally with the remaining

ingredients of the base such as the plasticizer, fillers, the bulking agent and/or sweeteners, the softener and coloring agents to plasticize the blend as well as to modulate the hardness, viscoelasticity and formability of the base. The chewing gum base is then blended with the oral clinically effective anti-plaque, anti-gingivitis composition of the present invention which may have been previously blended with other traditional ingredients. Mixing is continued until a uniform mixture of gum composition is obtained. Thereafter the gum composition mixture may be formed into desirable chewing gum shapes.

In accordance with this invention, dental hygiene therapeutically effective amounts of the oral anti-plaque, anti-gingivitis composition of the present invention may be admixed into chewing gum products. These amounts are readily determined by those skilled in the art without the need for undue experimentation. In a preferred embodiment of the present invention, the therapeutic anti-plaque, anti-gingivitis chewing gum compositions comprise in percentages by weight (1) at least one essential oil such as thymol, eucalyptol or peppermint in a total amount from about 0.01% to about 0.4%, (2) benzoic acid in an amount from about 0.005% to about 3.0%, and (3) an antimicrobial quaternary ammonium salt as illustrated by but not limited to, cetylpyridinium chloride, benzalkonium chloride,

benzethonium chloride, domiphen bromide, 1-(3-chlorallyl)-3,5,7-triaza-1-azoniaadamantane chloride, or menthene ammonium chloride in an amount from about 0.01% to about 10%.

In a more preferred dental hygiene chewing gum embodiment, the therapeutic anti-plaque, anti-gingivitis composition comprise in percentages by weight (1) at least one essential oil such as peppermint oil, eucalyptol or thymol in a total amount from about 0.03% to about 0.2%, (2) benzoic acid in an amount from about 0.10% to about 0.5% and (3) cetylpyridinium chloride in an amount from about 0.05% to about 0.3%.

The present invention extends to methods of making the improved oral anti-plaque, anti-gingivitis composition for chewing gum. The clinically effective, therapeutic anti-plaque, anti-gingivitis composition according to the present invention may be incorporated into an otherwise conventional chewing gum composition using standard techniques and equipment known to those skilled in the art. The apparatus useful in accordance with the present invention comprises mixing and heating apparatus well known in the chewing gum manufacturing arts, and therefore the selection of the specific apparatus will be apparent to the artisan.

The present invention is further illustrated by the following examples which are not included to limit the effective scope of the claims. All parts and percentages in the examples and throughout the specification and claims are by weight of the final composition unless otherwise specified.

STUDY "A"

The plaque reducing efficacy of the mouthrinse composition according to the present invention has been compared to a 0.12% chlorhexidine rinse (Peridex®, Proctor & Gamble), the comparative formulations were applied prior to conventional manual toothbrushing in a once daily, single use regimen. Moreover, a twice daily regimen was followed to demonstrate the cumulative plaque reduction efficacy of the preferred mouthrinse embodiment of the present invention (CPC/essential oil) as compared to the well-known 0.12% chlorhexidine product (as identified above) which served as a performance standard and a placebo control. Finally, the results obtained at 5 days of trial were also evaluated as to whether there could be a basis with regard to predictability of the 6-week treatment result.

The investigation was performed in the form of a three phase double blind, controlled clinical trial. In short, human subjects with a plaque index $\geq$1.95 following

8-10 hours of no oral hygiene qualified for the study. The efficacy results are listed on the Efficacy Table 1.

TABLE I (EFFICACY)

	MEAN±SEM			
	Example #1	Example #2	Example #3	P Value
Post-Brushing				
Adjusted Mean	2.24±0.05	2.22±0.04	2.15±0.05	0.38
Unadj. Mean	2.24±0.05	2.24±0.05	2.08±0.06	----
Baseline Mean	2.67±0.05	2.65±0.05	2.57±0.05	0.39
% Change	15.0±1.93	15.5±1.65	18.1±1.79	0.39
Day 5				
Adjusted Mean	1.10±0.14	1.48±0.10	1.71±0.10	<.01
Unadj. Mean	1.35±0.08	1.51±0.08	1.75±0.07	----
Baseline Mean	2.67±0.05	2.65±0.05	2.57±0.06	0.39
% Change	59.9±5.43	42.8±3.84	34.9±4.01	<.01
Week 6				
Adjusted Mean	1.79±0.13	1.88±0.10	2.17±0.09	<0.05
Unadj. Mean	1.88±0.08	2.06±0.07	2.18±0.06	----
Baseline Mean	2.67±0.05	2.65±0.05	2.57±0.06	0.39
% Change	32.8±4.81	28.9±3.76	17.8±3.50	<.05
Repeated Measures Analysis				
Adjusted Mean	1.74±0.09	1.82±0.07	2.01±0.06	<.05
Unadj. Mean	1.82±0.06	1.94±0.05	2.01±0.05	----

Test Solutions were designated as follows:

Ex. #1.: CPC/Essential Oils

Ex. #2: Chlorhexidine Solution

Ex. #3: 5% Hydroalcohol Solution

In Phase 1, of the study subjects received a baseline plaque exam and were randomly assigned to either a group testing the inventive composition mouthrinse (Example #1), the Comparative Product (Example #2) or the negative control Example. Subjects rinsed under supervision for 30 seconds with 15 ml of their assigned rinse, brushed with a soft nylon toothbrush and dentifrice for 30 seconds, and rinsed with 15 ml of tap water for 30 seconds. Subjects were then rescored for plaque. In Phase 2, subjects received a complete dental prophylaxis and began twice daily unsupervised rinsing with 15 ml of their assigned rinse for 30 seconds prior to brushing with a dentifrice in their usual manner. In Phase 3, subjects were rescored for plaque on day 5. Subjects continued with their respective regimens and were rescored for plaque at the end of 6 weeks.

One hundred and seventy-four (174) subjects completed the single-use phase, 159 completed 5 days' use, and 151 completed 6 weeks' use. The experimental Example #1 and positive control Example #2 were not significantly more effective than the negative control of Example #3 when

used prior to toothbrushing in the single use trial; however, Example #1 was significantly more effective than control Example #3 following five days and six weeks of unsupervised use. Comparative Example #2 was significantly more effective than the control Example #3 mouthrinse after 5 days of twice daily unsupervised use, but was not significantly more effective than the control mouthrinse at 6 weeks. The percent reductions vs control at 6 weeks for the inventive Example #1 rinse and the comparative Example #2 rinse were 18% and 13%, respectively. Under the conditions of this study the results obtained following 5 days were not consistently predictive of 6-week results. Although the 5-day and 6-week results were comparable in the Example #2 rinse group, there was considerable difference in the 5-day and 6-week results in the Example #1 rinse group.

The composition of the especially preferred embodiment (Example #1) of the present invention as tested is presented in Table II as follows by weight:

TABLE II

Peppermint Oil	0.050%
Thymol	0.064%
Eucalyptol	0.092%
Cetylpyridinium Chloride	0.100%
Alcohol	21.0%
Flavors	0.595%
Propylene Glycol	14.00%

Poloxamer 407	0.10%
Benzoic Acid	0.15%
Sodium Saccharin	0.15%
Colors	0.023%
Sorbitol Solution	30.000%
Water Adjust to	100.00%

Systemically healthy male and female adult volunteers, age 18-55, were selected who had a minimum of 20 sound, natural teeth and a mean Quigley-Hein plaque Index (Turesky modification) score $\geq$1.95 following 8-10 hours of no oral hygiene. (Turesky, S., Gilmore, N.D. and Glickman, 1.: "Reduced plaque formation by the chloromethyl analogue of Vitamin C J. Periodontal. 41:41-43, 1970.) Grossly carious, fully crowned or restored, orthodontically banded, abutment and third molar teeth were not included in the tooth count. Subjects with advanced periodontitis, gross oral pathology or an antibiotic, anticoagulant, or antiinflammatory therapy were excluded from the study.

Subjects were assigned to either the Example #1, Example #2 or Example #3 mouthrinse group according to a computer-generated random code. Each subject was assigned a number by a representative of the principal investigator but the product group assignment was not disclosed to either the principal investigator, examiner or recorder. All rinses were provided in individually-coded bottles.

SINGLE USE EVALUATION (PHASE 1)

Subjects refrained from all oral hygiene and use of any mouthrinse for 8-10 hours prior to the baseline examinations. Following a soft tissue examination, subjects rinsed with a disclosing solution and baseline plaque index scores were. Subjects then rinsed under supervision with 15 ml of their assigned rinse for 30 seconds and brushed for a timed 30 seconds with the soft nylon brush and fluoride dentifrice. Immediately following brushing, subjects rinsed thoroughly with 15 ml of tap water for 30 seconds and were redisclosed and scored for plaque. Rinsing and brushing were conducted in the absence of the examiner in order to maintain blinding. No mirrors were present in the area in which subjects brushed.

EVALUATION OF CUMULATIVE PLAQUE REDUCTION EFFICACY (PHASES 2&3) (Table I)

One week following the single use phase, subjects received a complete supragingival dental prophylaxis, which included scaling and a rubber cup polishing with prophylaxis paste, to render the tooth clinical crowns plaque free, as confirmed with disclosing solution. Subjects were provided with individually coded 16 oz.

bottles of their assigned rinse and graduated plastic cups for unsupervised home use. Subjects were instructed to rinse with 15 ml of their assigned rinse for 30 seconds prior to brushing twice daily for 6 weeks, starting the same day as the prophylaxis. At least 4 hours were to elapse between the two daily rinsings/brushings. Subjects received an intraoral soft tissue examination and were disclosed and scored for plaque after 5 days (Phase 2) and 6 weeks (Phase 3) of unsupervised rinsing, following an 8-10 hour period of no oral hygiene.

All used bottles were returned weekly to the supervision who recorded the volume of remaining mouthrinse to estimate compliance. Subjects also maintained a daily diary of rinsings which became part of the record. during the study, subjects followed their usual oral hygiene and dietary habits using the Oral B 35P soft nylon toothbrush and ADA-approved fluoride dentifrice provided. Subjects refrained from use of commercial mouthrinses and were instructed to inform the investigator of any antibiotic or antiinflammatory drug use during the study.

Subjects refrained from all oral hygiene and use of mouthrinses for 8-10 hours prior to the examinations at baseline, 5 days, and 6 weeks. A complete intraoral soft tissue examination was performed at baseline, 5 days, and 6 weeks to record the condition of the oral mucosae. Buccal

and lingual mucosae, tongue, hard and soft palate, uvula and oropharynx were examined for inflammation, infection, ulcerations or other lesions. Aberrations were recorded, their severity assessed and a judgment made as to whether or not they were attributable to the test materials.

Plaque area was scored on the buccal and lingual surfaces of all scorable teeth during Phase 1, at baseline and following a single rinsing and brushing, and during Phases 2 and 3, following 5 days' and 6 weeks' product use, respectively, using the aforementioned Turesky modification of the Quigley-Hein Index after disclosing with a D&C Red #28 solution.

The grading system was defined as follows:

0 - no plaque.
1 - separate flecks or discontinuous band of plaque at the gingival (cervical) margin.
2 - thin (up to 1 mm), continuous band of plaque at the gingival margin.
3 - band of plaque wider than 1 mm but less than 1/3 of surface.
4 - plaque covering 1/3 or more, but less than 2/3, of surface.
5 - plaque covering 2/3 or more of surface.

All examinations were performed by a single qualified dental examiner who reviewed the index with a representative of the sponsor prior to initiation of the study.

STATISTICAL ANALYSIS

The three treatment groups were evaluated for homogeneity with regard to age, sex, and smoking practices at baseline. To test for efficacy of treatments, a repeated measures analysis of variance with baseline values as the covariate was utilized to study differences between treatments over the course of the study. The Dunnett's test was used throughout the analysis to compare the test rinses Example #1 and Example #2 against the control (Example #3). Probability values of less than 0.05 were considered statistically significant.

There was one product related adverse reaction noted during the study for a subject rinsing with Example #2 which was consistent with an allergic reaction. A review of subject diaries indicated that out of 84 total unsupervised rinses, 16 subjects missed one rinse, 3 subjects missed 2 rinses, and 1 subject missed 3 rinses.

DEMOGRAPHICS

The treatment groups were well balanced at baseline for age, sex and smoking status (Table I). There were no significant interactions between any of these factors and treatments utilized.

TABLE II
DEMOGRAPHIC SUMMARY

TREATMENT GROUP	N	MEAN AGE	SEX MALES	SEX FEMALES	SMOKING YES	SMOKING NO
CPC/ESSENTIAL OILS	59	35.6	15	44	9	50
PERIDEX	60	33.2	12	48	14	46
CONTROL	55	35.2	11	44	11	44
TOTAL	174	34.6	38	136	34	140

There were no significant differences in mean baseline plaque scores between any groups ($p = .39$). An oral examination of subjects involve a single-use in Phase 1 followed by toothbrushing demonstrated that the Example #1 mouthrinse group had a 15 % reduction in supragingival plaque, the comparative Example #2 mouthrinse group a 16% reduction and the Example #3 mouthrinse control group a 18% reduction compared to baseline. There was no statistically significant difference between the experimental Example #1 oil rinse, the comparative product Example #2, or the control rinse (Example #3) ($p = .38$).

The unadjusted mean plaque scores and percent reductions vs baseline were:

TREATMENT GROUP	N	BASELINE	POSTBRUSH	% REDUCTION FROM BASELINE
Ex. #1	59	2.67	2.24	15%
Ex. #2	60	2.65	2.24	16%
Ex. #3	55	2.57	2.08	18%

Both the Example #1 and Example #2 mouthrinse were significantly more effective than control (Example #3) in reducing supragingival plaque following 5 days of unsupervised rinsing (Phase 3). The percent reductions versus control were 36% and 14% for the Example #1 and Example #2 groups, respectively.

The adjusted mean plaque scores and percent reductions vs control at 6 weeks of Phase 3 were:

TREATMENT GROUP	N	MEAN SCORE (S.E.)	% REDUCTION VS CONTROL
Ex. #1	52	1.79 (0.13)	18%*
Ex. #2	49	1.88(0.10)	13%
Ex. #3	50	2.17(0.09)	--

*Significantly more effective than control ($p<.05$)

Statistical analysis indicated that the inventive embodiment, Example #1 mouthrinse was significantly more effective than control ($p<.05$) between the comparative control mouthrinses of Example #2 and Example #3. The

percent reductions versus control were 18% and 13% for the Example #1 and Example #2 rinse groups, respectively.

Although chlorhexidine solution (Example #2) was included as a positive control for assessing cumulative anti-plaque activity, it should be noted that it is usually used as a "post-brushing rinse." In this study, the Example #2 product was significantly more effective than the negative control at 5 days, but was not statistically different from control at 6 weeks. The inclusion of a 5-day examination was based on recently reported short-term studies of a triclosan-containing prebrushing rinse which demonstrated that formulation to have significant plaque reduction efficacy when used twice daily for 5 days prior to toothbrushing. Singh, S.M. et al.: "Effect of a mouthrinse containing triclosan and a copolymer on plaque formation in a normal oral hygiene regimen". Am. J. Dent. 3:S63-S65, 1990; Rustogi, K.N., et al.: "Clinical study of a pre-brush rinse and a triclosan/copolymer mouthrinse: Effect on plaque formation". Am. J. Dent. 3:S67-S69, 1990. Since a 5-day study incorporating normal oral hygiene is of somewhat shorter duration than studies traditionally used to support a mouthrinse's anti-plaque efficacy, the current study determined the relationship of results at 5 days to those following 6-weeks' use. The 5 day results reported above were not consistently predictive of findings after

more prolonged use. Although the 5-day and 6-week results in the comparative Example #2 group were comparable, there was considerable difference in the 5-day and 6-week results in the experimental Example #1 group.

There was no significant difference between the experimental mouthrinse (Example #1), the comparative product (Example #2), and a negative rinse control (Example #3) in a single-use trial. However, the experimental Example #1 rinse was significantly more effective than the Example #3 control when used prior to usual toothbrushing following 5 days and 6 weeks of twice daily unsupervised use. The mouthrinse of Example #2 was significantly more effective than the control solution of Example #3 following 5 days' use, but not at 6 weeks. Under the conditions of this study, it was apparent that the results obtained at 5 days were not consistently predictive of the 6 week results.

Further, a study on the in vivo efficacy of the aforementioned most preferred composition for a cetylpyridium chloride (CPC)/essential oil mouthrinse in inhibiting the development of supragingival dental plaque. In particular, the study ranged over a 4-day period with no oral hygiene. The results of (Study B) are summarized below.

COMPARATIVE STUDY "B"

Test solutions were as follows:

Example #4 - cetylpyridinium chloride/essential oil mouthrinse (see composition above)

Example #5 - triclosan (0.03%) mouthrinse (Antibrush-Colgate), comparative positive control

Example #6 - Chlorhexidine (0.2%), (Corsodyl-ICI), positive comparative control

Example #7 - Hydroalcohol (5%) negative comparative control

Fifteen healthy adult subjects completed a double-blind, crossover design clinical study to compare the in vivo anti-plaque efficacy of a mouthrinse having the most preferred anti-plaque, anti-gingivitis composition according to the present invention, Example #4, with that of Example #5 mouthrinse an Example #6 mouthrinse, and a negative control (Example #5) using a no oral hygiene plaque regrowth model (see M. Addy et al. 1983, J. Clin. Periodontal. 10:89-98).

Subjects received a thorough oral prophylaxis to remove all plague from the teeth and then rinsed twice daily under supervision with their randomly assigned mouthrinse for 4 days. No other forms of oral hygiene were permitted during this 4 day period. On day 5, subjects

received an oral soft tissue examination and plaque levels were scored using both a plaque index (Turesky modification of the Quigley-Hein Plaque Index) and planimetry. After a washout period of at least 48 hours, subject were given another prophylaxis, were randomly assigned the next mouthrinse, and were reexamined following twice daily rinsing under supervision for 4 days. This regimen was repeated until each subject tested each of the mouthrinses.

When used as the only oral hygiene measure, rinsing with the mouthrinses of Example #4 through #6 resulted in significant plaque reductions ($p < .001$) of 43.6%, 25.1% and 66.0%, respectively, as compared to the negative control of Example #7 as determined using the plaque index. Planimetry results showed significant plaque reductions ($p < .001$) of 74.7%, 55.6% and 89.4% for the CPC/essential oil, triclosan, and chlorhexidine mouthrinses, respectively. Example #1 mouthrinse according to the most preferred composition of the present invention was significantly more effective ($p < .001$) than the mouthrinse of Example #5.

The results of this study demonstrate that the CPC/essential oil mouthrinse is effective in inhibiting the development of supragingival plaque <u>in vivo</u> when used as the sole oral hygiene method.

WHAT IS CLAIMED IS:

1. A dental hygiene composition comprising at least one essential oil and at least one antimicrobial quaternary ammonium salt detergent.

2. The dental hygiene composition of claim 1 wherein the essential oils are selected from the group consisting of menthol, eucalyptol, carvone, anethole, eugenol, isoeugenol, methyl salicylate, limonene, osimen, n-decyl alcohol, citronel, *a*-salpineol, methyl acetate, peppermint oil, spearmint oil, cinnamon oil, clove oil, and rosemary oil.

3. The dental hygiene composition of claim 1 wherein the essential oils are peppermint oil, thymol and eucalyptol.

4. The dental hygiene composition of claim 1 wherein the antimicrobial quaternary ammonium salt detergent is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, domiphen bromide, 1-(3-chlorallyl)-3,5,7-triaza-1-azoniaadamantane chloride and menthene ammonium chloride.

5. A liquid dental hygiene formulation for use without mechanical cleaning comprising, in a suitable oral vehicle, at least one essential or volatile oil, a antimicrobial quaternary ammonium salt detergent, ethyl alcohol, propylene glycol, nonionic surfactants, benzoic acid, sorbitol, artificial sweetener, flavoring agents, colorants, and water.

6. The liquid dental hygiene formulation of claim 5, wherein the antimicrobial salt is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, domiphen bromide, 1-(3-chlorallyl)-3,5,7-triaza-1-azoniaadamantane chloride and menthene ammonium chloride.

7. A mouth wash or mouth rinse solution comprising the dental hygiene composition of claim 1 as a therapeutically effective anti-plaque, anti-gingivitis agent before or after brushing.

8. The mouthwash or mouthrinse solution of claim 7 wherein the essential oil is by weight in the range of 0.02% to about 1.0%; the antimicrobial detergent is by weight in the range of about 0.005% to about 8%.

9. An improved anti-plaque, anti-gingivitis solution comprising the composition of claim 1, the improvement being a clinically efficacious cumulative reduction of calculus by rinsing treatment in the absence of brushing.

10. A clinically effective treatment of gingival inflammation and bleeding due to calculus buildup comprising applying the dental hygiene formulation of claim 5 as an oral rinse or wash without resort to mechanical scrubbing.

11. An improved anti-plaque, anti-gingivitis effective chewing gum composition comprising at least one essential oil and at least one antimicrobial quaternary ammonium salt detergent.

12. The improved anti-plaque, anti-gingivitis effective chewing gum of claim 11 wherein the total essential oil concentration ranges from about 0.01% to about 0.4%; and the antimicrobial quaternary ammonium salt detergent ranges from 0.01% to about 10%.

13. The improved anti-plaque, anti-gingivitis effective chewing gum of claim 11 wherein the essential oils are selected from the group consisting of menthol, eucalyptol, carvone, anethole, eugenol,

isoeugenol, methyl salicylate, limonene, osimen, n-decyl alcohol, citronel, a-salpineol, methyl acetate, peppermint oil, spearmint oil, cinnamon oil, clove oil, and rosemary oil.

14. The improved anti-plaque, anti-gingivitis effective chewing gum of claim 11, wherein the essential oils are peppermint oil, thymol and eucalyptol.

15. The improved anti-plaque, anti-gingivitis effective chewing gum of claim 11 wherein the antimicrobial quaternary ammonium salt detergent is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, domiphen bromide, 1-(3-chlorallyl)-3,5,7-triaza-1-azoniaadamantane chloride and menthene ammonium chloride.

16. A method for removing or preventing deposit of calculus by oral treatment with the dental hygiene composition of claim 1.

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/US 94/01316

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K7/22 A23G3/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K A23G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 098 476 (COLGATE PALMOLIVE COMPANY) 24 November 1982 see page 5; example 6a ---	1,2,4-10
X	EP,A,0 439 335 (COLGATE PALMOLIVE COMPNY) 31 July 1991 see page 4, line 31 - line 35 see page 4, line 45 - line 53 see page 5; example 2 ---	1-9
X	US,A,4 574 081 (SHYMON S.) 4 March 1986 see column 7; example 1 ---	1,2,4-9
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 July 1994	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Boulois, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 94/01316

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,93 08792 (WARNER LAMBERT COMPANY) 13 May 1993 see page 6, line 34 - page 7, line 18 see page 8, line 10 - line 24 see page 8, line 32 - line 34 see page 11, line 2 - line 4	1-10
X	DATABASE WPI Section Ch, Week 8429, Derwent Publications Ltd., London, GB; Class A10, AN 84-180136 & JP,A,59 101 417 (LION CORP.) 12 June 1984 see abstract	1,2, 4-13,15, 16
X	& PATENT ABSTRACTS OF JAPAN vol. 8, no. 218 (C-245)4 October 1984 & JP,A,59 101 417 (RAION KK) 12 June 1984 see abstract	1,2, 4-13,15, 16
X	DE,A,10 37 074 (SCHERING AG) 21 August 1958 see column 3; example 5	1,2,4-9
A	EP,A,0 244 363 (WARNER LAMBERT COMPANY) 4 November 1987 see page 7 - page 8; example 4	11-16
A	US,A,5 015 464 (STROBRIDGE J.) 14 May 1991 see column 2, line 20 - line 36	1-16
A	FR,A,2 320 083 (SIGMA TAU INDUSTRIE FARMACEUTICE RIUNITE SPA) 4 March 1977 see page 2; example 4	11-16

1

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Intern ...al Application No
PCT/US 94/01316

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-2098476	24-11-82	CA-A-	1183457	05-03-85
		DE-A-	3217379	03-02-83
		FR-A,B	2505654	19-11-82
		JP-B-	2039485	05-09-90
		JP-A-	57192311	26-11-82
		US-A-	4423030	27-12-83
EP-A-0439335	31-07-91	US-A-	5256396	26-10-93
		AU-B-	637179	20-05-93
		AU-A-	6936091	25-07-91
		DE-D-	69102147	07-07-94
		JP-A-	4210907	03-08-92
US-A-4574081	04-03-86	AT-B-	388294	26-05-89
		AU-B-	582386	23-03-89
		AU-A-	4760285	10-04-86
		BE-A-	903297	24-03-86
		CA-A-	1262687	07-11-89
		CH-A-	671335	31-08-89
		DE-A-	3533492	10-04-86
		FR-A-	2570601	28-03-86
		GB-A,B	2164849	03-04-86
		JP-A-	61085310	30-04-86
		NL-A-	8502613	16-04-86
		SE-A-	8504378	26-03-86
WO-A-9308792	13-05-93	US-A-	5298238	29-03-94
		AU-A-	2775392	07-06-93
DE-A-1037074		NONE		
EP-A-0244363	04-11-87	AU-B-	582047	09-03-89
		AU-A-	7187887	05-11-87
		JP-A-	62289511	16-12-87
US-A-5015464	14-05-91	NONE		
FR-A-2320083	04-03-77	NONE		